Onychomycosis of Toenails and *Post-hoc* Analyses with Efinaconazole 10% Solution Once-daily Treatment

Impact of Disease Severity and Other Concomitant Associated Factors on Selection of Therapy and Therapeutic Outcomes

JAMES Q. DEL ROSSO, DO, FAOCD

Clinical Professor (Dermatology), Adjunct Faculty, Touro University College of Osteopathic Medicine, Henderson, Nevada; Private Practice, Lakes Dermatology, Las Vegas, Nevada; Research Director, Del Rosso Dermatology Research Center, Las Vegas, Nevada

ABSTRACT

Topical treatment for toenail onychomycosis has been fraught with a long-standing reputation of poor efficacy, primarily due to physical properties of the nail unit that impede drug penetration. Newer topical agents have been formulated as solution, which appear to provide better therapeutic response in properly selected patients. It is important to recognize the impact the effects that mitigating and concomitant factors can have on efficacy. These factors include disease severity, gender, presence of tinea pedis, and diabetes. This article reviews results achieved in Phase 3 pivotal studies with topical efinaconazole 10% solution applied once daily for 48 weeks with a focus on how the aforementioned factors influenced therapeutic outcomes. It is important for clinicians treating patients for onychomycosis to evaluate severity, treat concomitant tinea pedis, address control of diabetes if present by encouraging involvement of the patient's primary care physician, and consider longer treatment courses when clinically relevant.
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Onychomycosis (ON) of the toenails is a very common fungal infection that predominantly affects adults.[1,2] In most cases, the fungal pathogen, usually a dermatophyte of *Trichophyton spp.* that is present within adjacent periungual skin of the toes, gains access to the nail unit distally by invading past the hyponychium into the nail bed and the adjacent ventral surface of the nail plate.[1–6] The large toenails are most commonly affected clinically; however, other toenails commonly exhibit visible changes characteristic of ON. Concomitant tinea pedis is often present as a source of the fungal pathogen; however, it may be subtle and considered by the patient or a clinician to be dry skin.[6]

Unlike many superficial infections involving glabrous skin, ON is well known as a disorder that is difficult to treat effectively due to the slow growth of the nail plate and the physical characteristics of the nail unit that impede drug penetration and access to the site of infection. In addition, host factors are recognized that can markedly influence therapeutic outcomes when treating ON. These include age, individual nail growth rate, overall health status, immune status, underlying medical disorders, pre-existing trauma-induced nail changes, and genetic predisposition to carriage of *Trichophyton rubrum* on pedal skin.[1–8] By the time ON has become visible, the pathogen has gained significant access to the nail bed, enough to induce physical changes, such as onycholysis, discoloration, hyperkeratosis, and plate thickening.[6] Over time, the severity of involvement progressively increases with greater proximal extension in affected nails and involvement of additional nails. Toenail ON often starts visibly by affecting only one or two nails, usually large toenails, and often spreads to other toenails.

As the severity of physical changes increases, ON

DISCLOSURE: Dr. Del Rosso serves as a consultant (C) and/or speaker (S) for several companies that currently market and/or are developing antifungal products including products used for management of onychomycosis and/or other nail disorders, including Valeant [C,S] (efinaconazole topical solution, 10%), Anacor [C,S] (tavaborole 5% solution), PharmaDerm [C,S] (tavaborole 5% solution), Ranbaxy [C,S], and Viamet [C].
ADDRESS CORRESPONDENCE TO: James Q. Del Rosso, DO, FAOCD; E-mail: jqdelrosso@yahoo.com

becomes more recalcitrant, leading to nail plate thickening, destructive changes, and deformity.[3] Adverse sequelae of toenail ON include pressure-induced discomfort from overlying footwear, breakdown with erosion/ulceration of surrounding skin that is abraded or cut by dystrophic nail plate, and secondary bacterial infection developing within foci of surrounding skin that has become eroded or ulcerated.[3,6,7] Secondary bacterial infections and ulcerations of periungual toenail skin are more likely to lead to adverse sequelae in patients affected by concomitant disorders, such as diabetes, peripheral vascular disease, and peripheral neuropathy.

In this article, the author evaluates how disease severity and specific concomitant factors affect therapeutic outcomes when treating onychomycosis. An overview of ON with emphasis on toenail involvement and important correlations with treatment selection are also addressed.

OVERVIEW OF ONYCHOMYCOSIS WITH EMPHASIS ON TOENAIL INVOLVEMENT

Overall, publications report that toenail ON comprises approximately 50 percent of all nail disorders, is nearly always associated with tinea pedis, and is more prevalent in males, elderly people, patients with immune compromise such as HIV, and in those with diabetes.[3–7] Advancing age is the most prevalent predisposing risk factor for toenail ON, with some studies noting that 48 percent of the population may be affected by age 70.[6,7] The severity of ON is often described based on the extent (percentage) of visible nail plate involvement with grading as mild (<25%), moderate (26–74%), and severe (>75%).[4] Data from a prospective, multicenter survey of 15,000 patients with distal lateral subungual ON visiting physicians' offices in Canada identified 27.6 percent of patients as mild, 39.9 percent moderate, and 32.5 percent severe.[4] It has been suggested that the extent of toenail involvement, or the number of toenails involved, has not been shown to definitely offer any prognostic value with ON treatment.[8] However, as will be discussed later, pivotal, randomized, vehicle-controlled trials (RVCTs) of recently approved topical therapies (efinaconazole 10% solution, tavaborole 5% solution) have provided some reasonable guidance on the range of therapeutic success that may be anticipated with toenail ON presenting with up to 50- to 60-percent involvement (determined as percent of visible target toenail plate affected), nail plate thickening of <3 mm, and absence of matrix involvement.

WHO IS AFFECTED BY TOENAIL ONYCHOMYCOSIS?

Individuals, especially adults, of either gender and of any heritage, ethnicity, and skin color may be affected by ON. ON is less common in the pediatric population, and when present, is often dermatophyte toenail ON seen in children and adolescents from families affected by chronic dermatophytosis and pedal carriage of *Trichophyton spp.*, most commonly *T. rubrum*.[4,6–8]

Men have been reported to be up to three times more likely to have toenail ON than women, though reasons for this gender difference are not entirely clear.[4,7] Occupational factors,[4] increased use of occlusive footwear,[9] more frequent nail injuries,[9] and hormonal differences have all been implicated.[4] Although toenail ON has been reported overall to have a greater adverse impact on the quality of life of female patients, many male patients are bothered physically and/or psychosocially by toenail ON and are motivated with regard to treatment.[10,11]

TRANSLATION OF DATA FROM CLINICAL STUDIES TO "REAL WORLD" APPLICATION OF THERAPEUTIC AGENTS USED TO TREAT TOENAIL ONYCHOMYCOSIS

When assessing whether or not a topical or oral agent is likely to be effective in a given patient affected by ON, it is important to evaluate details related to study methodology. Examples of study-specific details to note include the patient population, inclusion and exclusion criteria, concomitant disease states, efficacy endpoints, study power, mean age, extent of involvement (% area of visibly affected nail plate), method(s) used to determine extent of disease, primary and secondary efficacy parameters, dosage, duration of disease, treatment duration, and side effects, especially those correlated with discontinuation of therapy. Any underlying disorders that mandate exclusion from the study, such as diabetes and immunocompromised conditions, must be taken into account as the presence or absence of these factors may markedly affect therapeutic outcomes. Studies that more carefully capture the rate of nail plate growth allow for improved correlation of clearance of ON with adequate duration of therapy, as successful therapy is dependent on complete outgrowth of the affected nail plate.

IN WHAT WAYS MAY CONCOMITANT FACTORS INFLUENCE TREATMENT SELECTION AND THERAPEUTIC OUTCOMES?

Both superficial and deep fungal infections are a major cause of morbidity and mortality in individuals with HIV infection, who when not effectively treated to reduce their viral load, exhibit marked immunosuppression.[12] Toenail ON in immunosuppressed patients, including those with HIV infection, may sometimes present with proximal subungual ON (PSO). Although proximal white subungual ON (PWSO) has been reported as an association with HIV infection, it may also occur in association with immunosuppression induced by other causes. The prevalence of ON in HIV-infected patients has been reported to be as high as 30 percent, and appears to be directly related to the severity of immunosuppression.[13]

The incidence of ON in adults with diabetes is higher than what occurs among adults without diabetes, with approximately one-third of diabetics afflicted with ON, especially older patients, males, and those with severe onychodystrophy.[14–16] Toenail ON can predispose diabetic patients to important morbidities, such as an increased risk for development of periungual and digital skin erosions/ulcerations, secondary infections, and limb

amputation.[15]

The impact of toenail ON on the patient may be under-appreciated, especially as the disorder persists over many years. In one quality-of-life (QoL) analysis, approximately 40 percent of patients with ON for more than 10 years reported pain and discomfort.[17] For many affected individuals the psychological and social limitations may result from the reaction of others to their visible nail dystrophy or the perception that others find it to be unsightly and associated with poor personal hygiene.[17–21] These effects are especially pronounced in women who are more commonly concerned about the appearance of their nails and report greater interference with their daily activities.[22]

Toenail ON may be treated with both oral and topical medication. However, traditionally topical medication has provided relatively low cure rates and long treatment duration.[23,24] Newer topical agents formulated as solutions have recently been approved by the United States Food and Drug Administration (FDA) for treatment of toenail ON caused by *T. rubrum* and *T. mentagrophytes* (i.e., efinaconazole and tavaborole) based on results achieved in pivotal studies.[25,26] Low surface tension of the solution vehicles allow for easier spreadability and unaided flow of the formulation within crevices between the nail plate and adjacent soft tissue and cuticle, and at the hyponychium where distal onycholysis related to the disease provides a portal of entry. This low surface tension property differs from a lacquer-based vehicle (i.e., ciclopirox), which stays in place and dries at the site where it is applied due to inherently greater viscosity. In addition to the conventional consideration of transungual nail plate penetration after topical application, the ability of the solution vehicle to easily migrate is felt to be relevant therapeutically as subungual penetration is likely to be a means of medication access to the site of infection when treating dermatophyte toenail ON. The ability of a topical formulation to achieve subungual penetration in adequate concentration is important as the predominant site of dermatophyte infection in most cases of toenail ON is the nail bed and contiguous ventral nail plate.[27]

One of the objectives of this review is to highlight recent clinical data gleaned from *post hoc* analyses of the Phase 3 pivotal studies performed with efinaconazole 10% solution applied once daily for toenail ON. Emphasis is placed on assessment of factors, which may have impact on treatment outcomes, such as severity of toenail ON at baseline and other concomitant conditions. The efficacy, safety, and tolerability of efinaconazole 10% solution was assessed in two multicenter, randomized, double-blind, vehicle-controlled Phase 3 studies (pivotal RCTs) inclusive of 1,655 subjects with toenail ON rated as mild to moderate in severity.[25] The *post hoc* analyses were completed based on data captured in these two studies with all subjects treated topically once a day for 48 weeks; final efficacy analysis was captured at 52 weeks (4 weeks off of therapy). In these two pivotal RCTs with topical efinaconazole 10 % solution, a complete cure was defined at Week 52 based on the following two FDA-mandated protocol components: 1) a normal-appearing target large toenail plate by investigator clinical assessment, that is, without any visible evidence of ON and 2) a mycologic cure based on two designated methods of laboratory evaluation. Mycologic cure was strictly defined as both a negative potassium hydroxide preparation (KOH) and a negative fungal culture with the specimens obtained at 52 weeks. The definition of another separate efficacy endpoint that was captured at 52 weeks, described as treatment success allowed for less than 10 percent of distal target toenail involvement based on clinical (visible) evaluation by the investigator and also required a mycologic cure as described above.[26] Subjects enrolled in these pivotal RCTs did not undergo periodic nail plate debridement, which differs from pivotal studies completed with topical ciclopirox 8% nail lacquer for toenail ON.[25,26]

TREATMENT OF MILD-TO-MODERATE ONYCHOMYCOSIS

Due to long-standing recognition of poor cure rates achieved with topical antifungal therapy for toenail ON, clinicians have historically used topical monotherapy usually in cases limited to milder disease severity.[7,27–29] In some cases, topical therapy for toenail ON was used purely as a palliative treatment attempt in patients who were not good candidates for or refused oral antifungal therapy. When the clinician is trying to translate in their mind the anticipated efficacy in clinical practice with a newer topical therapy for toenail ON, it is important to accurately visualize the clinical pattern and severity of toenail ON that was included in a given study. The visible pattern and severity of clinically evident nail dystrophy in the pivotal RCTs used for the *post hoc* analyses discussed here was distal involvement with up to 50 percent of the nail plate surface area clinically affected based on visible inspection and planimetry.[26] In addition, the FDA-approved protocol in these pivotal RCTs excluded enrollment of subjects with target toenail plate thickness >3mm, visible involvement of the nail matrix, and/or presence of dermatophytomas.[25,26]

Overall, three-quarters (74.8%) of the subjects with toenail ON in the two pivotal RCTs treated topically with efinaconazole 10% solution were graded as moderate severity at baseline. Approximately one-fourth (25.8%) of subjects treated topically with efinaconazole 10% solution entered the study with a severity rating of mild toenail ON at baseline.

Efinaconazole was effective for toenail ON with a complete cure rate of 18 percent in Study 1 and 15 percent in Study 2, versus three percent and six percent with vehicle, respectively ($P<0.001$).[26] Complete cure required mycologic cure (KOH and culture negative) and a visibly normal-appearing target large toenail plate at 52 weeks. Treatment success, defined as patients with mycologic cure and less than 10 percent distal target nail plate involvement by visible assessment after 52 weeks, were 45 percent in Study 1 and 40 percent in Study 2, versus 17 percent and 13 percent with vehicle, respectively. It is anticipated that complete cure rates would be higher in subjects with toenail ON of milder severity, as the "load of distal dystrophic nail

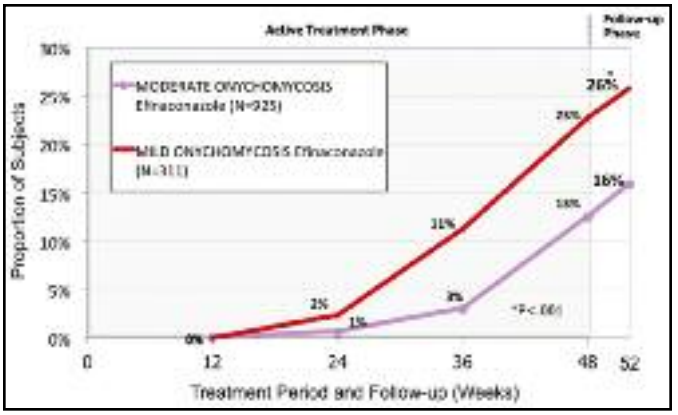

Figure 1. Mild and moderate onychomycosis: Primary efficacy endpoint complete cure at Week 12–52. Comparison of results with efinaconazole topical solution, 10% (ITT pooled data, observed case). Complete cure defined as 0% clinical involvement of target toenail in addition to mycologic cure.
Adapted from Rodriguez D. Efinaconazole topical solution, 10% for the treatment of mild and moderate toenail onychomycosis. *J Clin Aesthet Dermatol.* 2015;8(6):24–29.

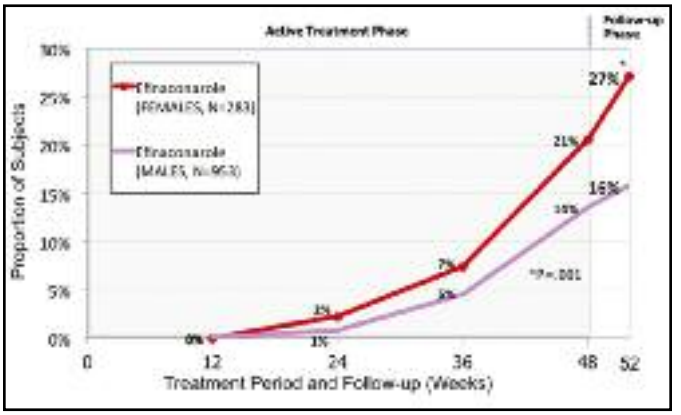

Figure 2. Male and female onychomycosis patients: Primary efficacy endpoint complete cure at Week 12–52. Comparison of results with efinaconazole 10% solution (ITT pooled data, observed case). Complete cure defined as 0% clinical involvement of target toenail in addition to mycologic cure.
Adapted from Rosen T. Evaluation of gender as a clinically relevant outcome variable in the treatment of onychomycosis with efinaconazole topical solution. *Cutis.* 2015;96(3):197–201.

plate" that needs to grow out to be cleared over time is less, and is more likely to be cleared with a 48-week duration of active treatment, even in some subjects with slower nail plate growth rates. This is especially important as actively growing large toenails sometimes require 78 weeks before full outgrowth occurs.[26] It is also interesting to compare the trajectories of the two patient populations that suggest moderate ON patients may require a longer treatment course (Figure 1).[26] Mycologic cure rates at study end were similar in both patient groups, and other studies have shown continued improvement in cure rates in ON patients with longer treatment courses.[30]

IS GENDER A CLINICALLY RELEVANT VARIABLE?

Efinaconazole 10% solution appears overall to be more effective in female subjects with toenail ON where more than 27 percent of patients achieved complete cures at Week 52 (P<0.001 versus the male patients) (Figure 2).[31] These data suggest that male patients may be more difficult to treat, although the reasons are unclear. It has been suggested that men tend to seek help for more advanced disease,[28,31] but in the efinaconazole pivotal RCTs, nail involvement was very similar in males and females. Adherence was better in the female cohort, a finding consistent with other gender studies. Although there is no evidence to suggest that male toenails grow quicker, they tend to be thicker and this fact could have impacted outcomes, although nails with a thickness >3mm were excluded from the clinical studies. It is possible that as the surface area of men's toenails are greater, infection takes longer to grow out perhaps requiring a longer treatment course, as suggested from the two trajectories in Figure 2.[31]

Differences seen in quality of life (QoL) at baseline were consistent with other findings in that toenail ON tends to have a more negative impact on QoL in female patients. That QoL was both improved and similar at study end probably reflects the better efficacy seen in females.

TINEA PEDIS AS A CONCURRENT DISORDER IN TOENAIL ONYCHOMYCOSIS

It is well recognized in dermatology practice that ON and tinea pedis can exist together in the same patient, tinea pedis can lead to ON, and it is important to evaluate and treat both diseases.[32] Onychomycosis has been found to be significantly more likely to be diagnosed in the context of tinea pedis (P<0.001),[33] with a history of tinea pedis more than doubling the risk of toenail ON.[34] Co-existing disease tends to be more prevalent in men, and it has been reported to increase with age.[35]

In the efinaconazole pivotal RVCTs, 21.3 percent of patients reported interdigital tinea pedis at baseline, a prevalence similar to that reported in previous surveys.[36] Treatment of toenail ON has been reported to be almost twice as successful when co-existing tinea pedis was also treated. Complete cure rates in this subgroup were 29.4 percent, compared with only 16.1 percent when the co-existing tinea pedis was not treated, supporting the importance of treating both conditions (Figure 3).[37] Mycologic cure rates were also greater in subjects with toenail ON where co-existing tinea pedis was treated.

COEXISTING DIABETES

It has been suggested overall that concomitant diabetes in a patient with toenail ON is associated with greater resistance to antifungal treatments as compared to non-diabetic patients, as high blood glucose levels and poor foot care can encourage fungal infection.[38,39] In the

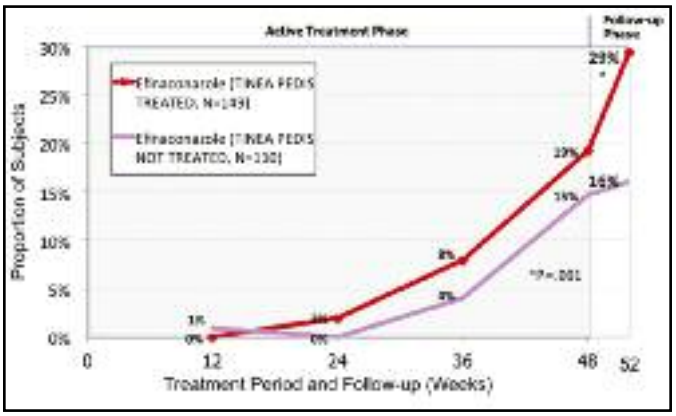

Figure 3. Onychomycosis patients with co-existing tinea pedis: Primary efficacy endpoint complete cure at Week 12–52. Comparison of results with efinaconazole 10% solution (ITT pooled data, observed case). Complete cure defined as 0% clinical involvement of target toenail in addition to mycologic cure.

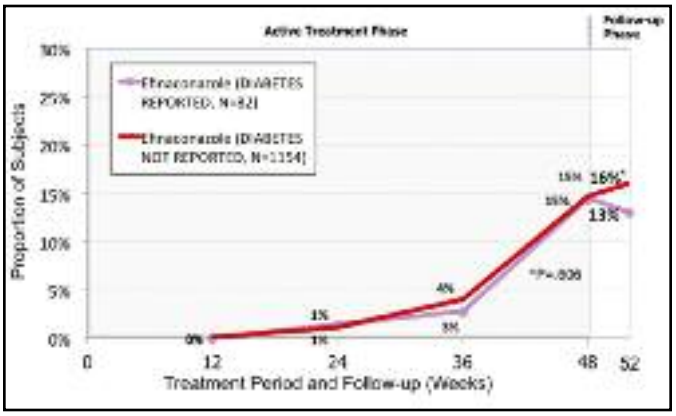

Figure 4. Onychomycosis patients with co-existing diabetes: Primary efficacy endpoint complete cure at Week 12–52. Comparison of results with efinaconazole 10% solution (ITT pooled data, observed case). Complete cure defined as 0% clinical involvement of target toenail in addition to mycologic cure.

aforementioned efinaconazole RVCTs, treatment cure rates were comparable in both the controlled diabetic and in the non-diabetic populations that were enrolled in the Phase 3 trials (Figure 4); note that uncontrolled diabetic patients are excluded from Phase 3 toenail ON trials.[39] Consistent with the findings of other workers, ON patients with co-existing diabetes tended to be older, with a greater proportion of male subjects and this tendency may explain the numerically higher (but not statistically significant) complete cure rates in the non-diabetic population. Mycologic cure rates at study end were similar in both patient groups.[39]

CONCLUDING REMARKS

Onychomycosis is a common fungal infection that can be difficult to treat successfully. Previously, topical therapy has usually been reserved for the mildest cases, primarily because of poor efficacy seen with these lacquer-based products. New topical agents formulated as solutions are now available. Efinaconazole topical solution 10% was found to be effective as monotherapy in mild and moderate disease. It may be that some patients with moderate and moderately severe toenail ON require a longer treatment course to achieve eradication of the infection. This may also be true when treating male patients as efinaconazole was more effective in female patients over the 48-week treatment regimen.

Treating co-existing tinea pedis is an important guiding principle in ON management, and the efinaconazole studies provide clinical data that clearly demonstrated the benefit of treating both conditions. The efinaconazole studies also showed that efficacy is not influenced by co-existing diabetic disease that is controlled. Interestingly, although complete cure rates continued to increase in the four-week follow-up period irrespective of severity or gender, when co-existing tinea pedis was not treated there was only minimal improvement after the 48-week treatment course.

In conclusion, efinaconazole topical solution 10% provides a topical treatment option for toenail ON that is effective, especially in properly selected patients, and with consideration of more prolonged therapy when severity is greater. Data suggest that a longer treatment course may be necessary in male patients and those with more severe disease. Treatment outcomes are significantly improved if co-existing tinea pedis is treated concurrently, and efficacy in patients with co-existing controlled diabetes does not appear to be compromised. As uncontrolled diabetic patients are excluded in Phase 3 toenail ON studies, it is not known what the effect on efficacy would be in this patient population.

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